REMARKS

Reconsideration of this application, in view of the below remarks and proffered evidence, is respectfully requested.

Applicants acknowledge with gratitude that the Examiner has dropped the rejection of Claim 4 under 35 U.S.C. § 112, first and second paragraphs, as well as the rejection of Claim 6 under 35 U.S.C. § 112, first paragraph.

The Examiner has maintained the rejection of Claims 1, 2 and 4-6 under the Judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-5 of U.S. Patent No. 6,340,691 for reasons of record and comments on page 2 of the Office action. It is noted that the Examiner had highlighted three compounds shown in Examples 3, 75 and 123 of the '691 patent as representing the closest art. Applicants respectfully traverse the rejection for the following reasons.

A close examination of the claims of the present application and the patented claims of the '691 patent would reveal unobvious structural differences that lead to unexpected, dissimilar physical, chemical and biological properties. In particular, the present claims state an exclusive proviso that one of the pairs of R_8 and R_9, R_9 and R_{10} or R_{10} and R_{11}, together with the carbon atom or atoms to which they are attached, must form a cycloalkyl ring of 3-6 carbon atoms, or a -C_4-C_8-cycloheteroalkyl ring. Thus, the present compounds are structurally distinct in two ways: (1) The carbon alpha to the hydroxamic acid group is always incorporated into a cycloalkyl or cycloheteroalkyl ring, while the compounds claimed in the '691 patent are not allowed or taught to form a ring at this position; and (2) an extra methylene has been inserted between the hydroxamic acid and the -$S(O)_2$ group.

Physically and chemically speaking, there are major differences seen. One advantage of the compounds of this invention over the '691 compounds is that they are achiral, while each patented compound contains a chiral center. The achiral structure eliminates the need for chiral separation or stereospecific synthesis to obtain a single enantiomer. The patented compounds of Examples 75 and 123 also have hydrogen that is alpha to the hydroxamic acid, making this an epimerizable center, while the present compounds do not possess the same structural feature. Furthermore, the constraint of the pair R_8 and R_9, R_9 and R_{10} or R_{10} and R_{11} into a cycloalkyl or cycloheteroalkyl ring in the present compounds dramatically decreases the conformational flexibility of this molecule.

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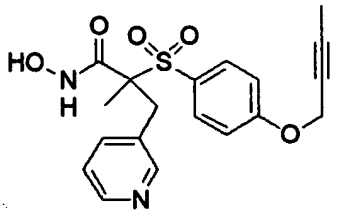
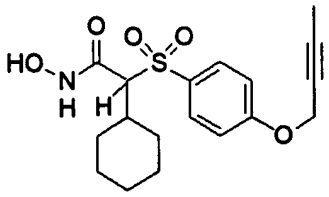
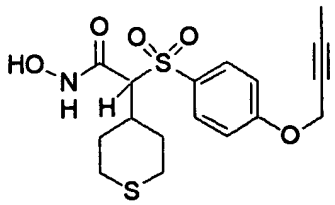
To visualize the physical distinctions, contrast the patented structures of Examples 3 (Art Compound A), 75 (Art Compound B) and 123 (Art Compound C) to the closest structure of the present application represented by Example 36 (Compound D) as shown below:



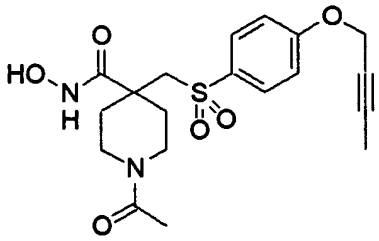
Art Compound A



Art Compound B



Art Compound C



Compound D (application)

In terms of the biological activity, the combination of the cycloalkyl or cycloheteroalkyl ring and the extra methylene of the compounds of the present invention also provides greater potency against the TACE enzyme in a cell-free assay and in a cellular assay, as compared to the closest art compounds. For the convenience of the Examiner, the biological data that were disclosed in the patent and described in the application are summarized below:

Compound	TACE[a]	THP[b]
Art Compound A	16	14
Art Compound B	27	39
Compound D	4.8	58

[a] IC_{50} (nM)
[b] % Inhibition at 3 μM

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By and large, the compounds of the present invention are more potent inhibitors of TACE than of MMP-1, MMP-9 and MMP-13 (see pages 128-130) while most of the art compounds demonstrate a greater potency towards inhibiting MMP-1 than against TACE (see cols. 72-73). Thus, the present compounds are selective TACE inhibitors in sharp contrast to the art compounds that may be described as selective MMP inhibitors.

A second extremely important difference in the biological activity is that Compound D of the present invention provides 58% inhibition of LPS-stimulated TNF production at 3 μM in THP-1 cells. In sharp contrast, the closest art compounds only give 14 and 39% inhibition in the same assay at 3 μM showing that the present compound possesses significantly improved cellular potency as a TACE inhibitor. Therefore, the cycloalkyl or cycloheteroalkyl ring and the extra methylene changes the selectivity profile and boosts the TACE enzyme and cellular activity of the present compounds over the closest art compounds.

As previously mentioned in the record, the physical, chemical and biological characteristics of the present compounds cannot be predicted from the prior compounds without undue experimentation and, therefore, the compounds of this invention cannot be considered an obvious variation of the patented compounds.

Moreover, slight structural differences can justify separate patents (*e.g.*, alkylene group between a ring and ester function of prior art compounds (*Ex parte Biel*, 124 U.S.P.Q. 109 (POBA 1958); *Ex parte Goonewardene et al.*, 160 U.S.P.Q. 288 (POBA 1968) and CH_2 between the CO and COOH of a -CO COOH group of a prior art compound, even in the absence of a showing of unexpected properties (*Ex parte Burtner et al.*, 89 U.S.P.Q. 547 (POBA 1950)). Under the circumstances in this case, the unexpected biochemical results and different physical properties make it highly unlikely that the chemist will be motivated to modify the patented compounds. The instant compounds are simply not a *prima facie* obvious variation.

In view of the foregoing remarks and proffered evidence, Applicants respectfully ask that the double patenting rejection be withdrawn.

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Accordingly, this application is now in condition for an allowance. Favorable treatment is respectfully urged.

Respectfully submitted,

WYETH HOLDINGS CORPORATION

Date: January 8, 2004

By: Anne M Rosenblum
Anne M. Rosenblum
Attorney for Applicants
Registration No. 30,419

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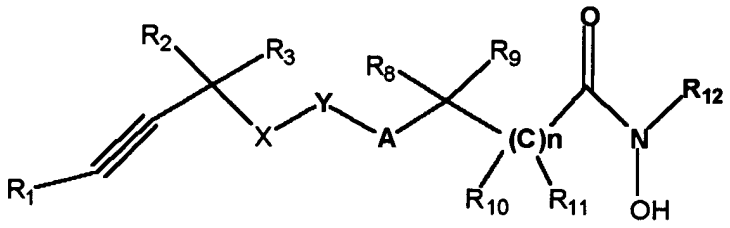
APPENDIX
AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

AMENDMENT TO THE CLAIMS

Claim 1 (Currently amended). A compound of formula



I

wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C4-C8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R_1, -SO_2-R_1, -C(O)-NHR_1, -C(O)NR_5R_6, -C(O)$R_1NR_5R_6$, -C(O)-OR_1, or -C(NH)-NH_2;

~~R_5 and R_6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl or -C4-C8-cycloheteroalkyl;~~

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs ~~R8 and R9, R9 and R10 or R10 and R11~~ R_8 and R_9, R_9 and R_{10} or R_{10} and R_{11}, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

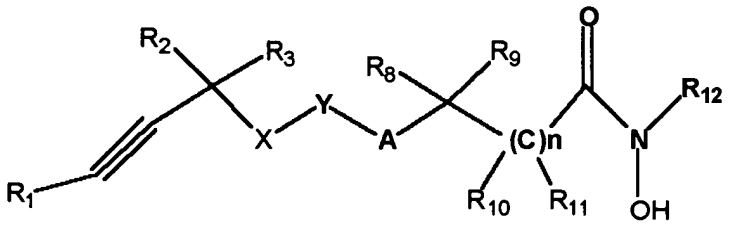
Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R_8 and R_9 together with the carbon atom to which they are attached may not form a piperdinyl or tetrahydropyranyl ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Claim 2 (Previously amended). A compound of Claim 1 wherein Y is phenyl, pyridyl, thienyl, furanyl, imidazolyl, triazolyl or thiadiazolyl.

Claim 3 (Cancelled).

Claim 4 (Currently amended). A method of treating a pathological condition or disorder which requires inhibition of TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula



I

wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C_4-C_8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R_1, -SO_2-R_1, -C(O)-NHR_1, -C(O)NR_5R_6, -C(O)R_1NR_5R_6, -C(O)-OR_1, or -C(NH)-NH_2;

R_5 and R_6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl or -C_4-C_8-cycloheteroalkyl;

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs ~~R8 and R9, R9 and R10 or R10 and R11~~ R_8 and R_9, R_9 and R_{10} or R_{10} and R_{11}, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

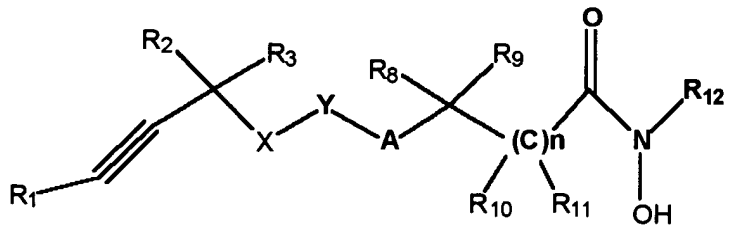
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R_8 and R_9 together with the carbon atom to which they are attached may not form a piperdinyl or tetrahydropyranyl ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

Claim 5 (Original). The method of Claim 4 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

Claim 6 (Currently amended). A pharmaceutical composition comprising a therapeutically effective amount of a compound having the formula



I

wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C_4-C_8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R_1, -SO_2-R_1, -C(O)-NHR_1, -C(O)NR_5R_6, -C(O)R_1NR_5R_6, -C(O)-OR_1, or -C(NH)-NH_2;

~~R_5 and R_6 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl or -C_4-C_8-cycloheteroalkyl;~~

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs ~~R8 and R9, R9 and R10 or R10 and R11~~ R_8 and R_9, R_9 and R_{10} or R_{10} and R_{11}, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C_4-C_8-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R_8 and R_9 together with the carbon atom to which they are attached may not form a piperdinyl or tetrahydropyranyl ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.